Research Paper Presentation

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Paper information

A review on colistin nephrotoxicity

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Introduction

- ***Colistin or polymixin E*** ;

- A **glycopeptide** antibiotic / was **discovered in 1949** / produced by a certain strain of a Bacillus polymixa variant called colistinus.

- Colistin became **available** for clinical use in the **1960s/ replaced** by less toxic antibiotics after almost a decade, **due to concerns** about its toxicity, **especially nephrotoxicity**

In the **past 10–15 years**, the emergence of multi-drug resistant **(MDR) gram negative bacilli**, especially *Pseudomonas aeruginosa, Acintobacter baumannii and Klebsiella pneumonia*, and the drying of the antibiotic development pipeline have **led to the return and increasingly world wide use of colistin**.

Colistin bactericidal effect is ***concentration-dependent*** /there exists a ***post-antibiotic effect*** against P.aeruginosa, A.baumannii and K.pneumonia.

Available forms of colistin:

- **Colistin sulfate** : for oral (bowel decontamination) and topical use.
- **Sodium colistimethate (CMS) :** for use via parenteral (IV) and inhalation routes .
- CMS is a less potent and less toxic prodrug of colistin.

Available brands of colistin for parenteral use:

Colymycin : labeled as **150 mg** colistin base activity (**CBA**), equivalent to **5,000,000** International Unit (**MIU**) or ***400 mg CMS***.

Colomycin : labeled as 500,000, 1,000,000 and 2,000,000 international units (IU) of CMS, equivalent to 40, 80, and120 mg of **CMS**.

Recommended dosage regimen:

Colymycin :***1–2 MIU of CMS every 8 hours*** (equivalent to 6 MIU or 480 mg CMS per day for maximum dose)

Colymycin : ***2.5–5 mg/kg/day of CBA*** in ***two to four divided doses*** (equivalent to 10 MIU or 800 mg CMS per day for maximum dose)

- **high-dose colistin therapy**: doses of approximately**≥9 MIU/day of CMS or≥5 mg/kg/day of CBA**

- The serum half-life of CMS : is approximately **1.5–2 hours after intravenous (IV) administration** and **2.75–3 h after intramuscular (IM)** administration in healthy subjects .

- Plachouras and colleagues demonstrated that with a **colistimethate** dose of **3 MIU (90 mg CBA) every 8 hours**, the **half-life of colistin was 14.4 hours** .

METHOD

Data was collected using **PubMed**, **Scopus** and **Cochrane** databases. The keywords used for the search were colistin, nephrotoxicity, toxicity, renal failure, high dose, and risk factor.

Randomized clinical trials and **prospective or retrospective observational animal and human studies** were included.

colistin nephrotoxicity and details regarding its mechanism of action and nephrotoxicity, the **definition of nephrotoxicity**, **biomarkers for detection and risk factors** of nephrotoxicity, and **modalities employed for prevention** of nephrotoxicity were **evaluated**.

38 related articles were retrieved on **colistin and nephrotoxicity**, **4 on colistin** nephrotoxicity and high dose,**12 on colistin and renal failure**, and **8 on colistin and risk factor**. A total of 60 articles were included for this review.

This review emphasizes dose-related nephrotoxicity of colistin.

For evaluation of the incidence of nephrotoxicity, articles in which high doses of colistin were administrated are summarized in Table 1.

High-dose colistin therapy is defined as approximately≥9 MIU/day of CMS or≥5 mg/kg/day of CBA.

Suggestion of a new dosing regimen :

Colistin **antibacterial** effect is **concentration dependent** and ***AUC/MIC*** is the ***best pharmacokinetic ratio*** that is *related to effective antimicrobial therapy* .

Example: optimal bactericidal effects against P. aeruginosa is when **AUC/MIC = 30** /another report a **ratio of Cmax/MIC ≥ 16** required for **complete** in vitro **killing** of P.aeruginosa **within 24 hours** / With *conventional doses, after 2–3 days of drug therapy*, a *steady state level* of *colistin* was obtained and an inacceptable AUC/MIC ratio led to failure of treatment.

- The **recommendation** is a **loading dose of 9 or 12 million units of CMS**, followed by maintenance doses of **4.5 million units twice daily.**

    - This recommendation raises concerns about the nephrotoxicity of colistin/ limits its administration /necessitates other trials for confirmation of the efficacy and evaluation of the prevalence and severity of nephrotoxicity.

Mechanism of action :

bactericidal effects of **colistin** :

1) **interaction** with a lipopolysaccharide (**LPS**) moiety of the membrane of Gram-negative bacteria, through **electrostatic interaction** and **cationic displacement (Ca and Mg)** of LPS ⟶ **disturbances** in the **stability** of the membrane & **increase** in its **permeability**, **leakage** of **cell content** and **cell Death**.
2) **Anti-endotoxin effect**: colistin binds to the **lipid A portion** of the lipopolysaccharide (**LPS**) molecule, the endotoxin of Gram-negative bacteria & **neutralizes it** .

Adverse drug reactions of colistin:

1) Nephrotoxicity : **more common** and concerning adverse effect /***dose-dependent*** / ***usually***, but not always, ***reversible***/ permanent kidney damage is rarely seen .

Manifestation: *decrease in clearance of creatinine*; **proteinuria**, **cylindruria or oliguria** may also occur.

- In a ***review*** of colistin toxicity in 2011, the ***prevalence*** of ***nephrotoxicity*** was different among trials and was reported to be in the range of ***0 to 53.5 %.***

Adverse drug reactions of colistin:

2) ***Neurotoxicity*** : **dose-dependent** and **reversible**

Manifestation: weakness, peripheral and facial *paraesthesia (most common = IV administration 27% & IM 7.3%)*, ***ophthalmoplegia***, *difficulty in swallowing*, *ataxia*, eyelid ptosis, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, rarely ***neuromuscular blockade*** leading to ***respiratory failure*** *(not been reported from 15years ago)* and the need for ventilatory support .

- Prevalence of ***neurotoxicity*** with polymixins is considerably ***less*** than ***nephrotoxicity***.

Sorli et al.

A prospective observational cohort study.

Aim: determination of the incidence and the risk factors of colistin nephrotoxicity.

patients>18 years were included if they had received CMS for more than 4 days/ 102 patients included/
(group 1): 28 (27.4 %) patients ,colistin : 1 MIU three times daily
(group 2) :42 (41.2 %) patients , colistin : 2 MIU three times daily
(group 3) : 16 (15.7 %) patients , colistin : 3 MIU three times daily
16 (15.7 %) patients, other doses(adjusted in accordance to renal function)

Results: prevalence of AKI at day 7 was 17.9 %, 26.2 % and 43.8 % for groups 1, 2 and 3, respectively. Prevalence of AKI at the end of treatment (EOT) day was 50 %, 50 % and 56.3 % for groups 1, 2 and 3, respectively.

Kalin and colleagues:

Aim: comparison of efficacy and nephrotoxicity of low, normal and high doses of colistin

45 patients were included,15 patients received high dose colistin (2.5 mg/kg every 6 h), 20 patients normal dose (2.5 mg/kg every 12 h), and 10 patients low dose, determined according to ***creatine clearance***.

The ***nephrotoxicity rate*** was **40 %, 35 %** and **20 %** for the **high**, **normal** and **low** dose of colistin.

Prevalence of colistin **nephrotoxicity** in the prospective study of **Dalfino and colleagues**, in which 28 patients were administered a colistin ***loading dose of 9 MU*** and ***maintenance*** doses of ***4.5 MU twice-daily***, was 17.8 %

Definition of nephrotoxicity of colistin:

Patients with ***normal renal function(serum creatinine<1.2)***: an **increase** in **serum creatinine** to a level o**f>2** /50 % reduction in calculated creatinine clearance in comparison with baseline value/ or a **decline in renal function** leading to **need for renal replacement therapy**.

Definition of nephrotoxicity of colistin:

patients with **pre-existing renal dysfunction**: **increase of serum creatinine** level equal to or more than 50 %/ a 50 % reduction in calculated creatinine clearance compared with baseline value/ **decline in renal function** leading to the **need for renal replacement therapy**.

- Creatinine clearance is to be calculated using the Cockroft and Gault formula.

Mechanism of nephrotoxicity:

CMS is **eliminated** mainly by **renal excretion**, and the urinary excretion involves renal tubular secretion. Colistin undergoes **extensive renal tubular reabsorption (up to 80 %)** and most of the filtered colistin is retained in the body, and is therefore cleared mainly by non-renal mechanisms.

- **Nephrotoxicity** of colistin is primarily related to: **d-aminobutyric acid** and **fatty acid components**.

Mechanism of nephrotoxicity :

similar to its antibacterial effect/

increase tubular epithelial cell **membrane permeability** → cations, anions and water influx → cell swelling and cell lysis.

Colistin = causes an **ATN** (manifested as a rise in serum creatinine and a decrease in creatinine clearance) & **proteinuria**, **cylindruria** and **oliguria**.

- This effect of colistin depends on the **concentration** and **length of exposure**.

There are also case reports of **acute interstitial nephritis** due to **hypersensitivity reactions to polymixines .Histological** findings of colistin-induced renal damage usually involve *focal irregular dilatation of tubules*, epithelial and polymorphonuclear cell cast formation, and degeneration and regeneration of epithelial cells. In addition, **separation** of tubules from the **surrounding tissues** has also been reported, which is suggestive of **edema**. The basement membrane is usually intact, as are the glomeruli.

Ozkan et al. study :

Aim : investigate the pathogenesis of **colistin-associated nephropathy**.

the role of **caspase-associated apoptosis** and **caspase1**, **calpain 1**, inducible nitric oxide synthase **(iNOS),** and endothelial nitric oxide synthase (**eNOS**) expression in the pathogenesis of colistin nephrotoxicity was investigated.

This study showed :**oxidative damage** was associated with an **increase** in **iNOS** and **eNOS**, and an increase in eNOS expression was parallel to **apoptotic injury** and thus **necrotic damage**.

increase in caspase 1 and 3, which are members of the cysteine protease family, was shown. **Caspase 3 is** activated as a result of the **activation** of the intrinsic and extrinsic apoptotic pathways and **leads to DNA breakdown**. Therefore, the authors suggested that **apoptosis** is involved in the pathogenesis of colistin nephropathy.

Caspase 1: an i**nflammatory** caspase/ recently been suggested to be **involved in apoptotic injury of cisplatin-induced kidney damage**/ an increase in caspase 1 staining in this study illustrated the involvement of caspase 1 in the nephropathy of colistin.

An increase in **calpain 1**, a **calcium-associated cysteine protease** involved in apoptotic and necrotic cell damage, indicates the likelihood of its involvement in the necrotic kidney injury of colistin.

Risk factors for nephrotoxicity:

The nephrotoxicity of colistin is sometimes reported as a rapid onset effect.

In **Deryke et al.'s study**, **all patients** developed nephrotoxicity in the **first 5 days** of treatment .

In the study **by Pogue et al**. the vast **majority** of toxicity also occurred **within the first week of treatment .**

In **Ko et al**.'s retrospective study, **AKI** with colistin occurred in **54.6** % of patients, with approximately **70 %** occurring **early** (**within 7 days**) in the course of treatment and the rest occurring late (after 7 days) in the course of treatment. The patients with **early AKI** had **a higher mortality** rate than those with late AKI .

- **Hartzell et al:** reported patients who **received CMS for more than 14 days** were **3.7** times more **likely to develop risk**, **injury** or **failure** of **RIFLE** criteria; the median day of stopping the therapy was 13.5 (range: 8–37), and the incidence of nephrotoxicity was not affected by other variables .

In Tuon et al.'s: retrospective cohort study, **receiving doses of≥2 MIU** of polymixin B (PMB) **or>9 MIU of CMS** was the **only variable independently associated with AKI** (associated with a twofold higher risk for AKI during treatment)/ also shown that **co-administration** of **vancomycin** significantly increased the incidence of AKI, and the mean baseline creatinine was lower in patients who developed AKI compared to those who did not. The median time from the start of therapy to the development of AKI was 7.5 days and there was no difference between patients treated with PMB and CMS .

Falagas and colleagues : showed, **concomitant** administration of **other nephrotoxic agents** was mentioned as a **probable risk factor** for **colistin nephrotoxicity** .

Kim et al.'s : case–control study, after adjustment for age, gender, hypoalbuminaemia, site of infection, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and cumulative dose of aminoglycosides or second generation fluoroquinolones , they found that the factors h**ypoalbuminaemia** and **concomitant use of NSAIDs** were **independent risk factors for nephrotoxicity**.

- In another study, **independent risk factors** of colistin nephrotoxicity after multi-variety analysis were **old age**, **long duration of intravenous colistin, high dose of intravenous colistin(>5 mg/kg/d) and concomitant vancomycin therapy**.

- **Rocco et al**. : in **severely ill ICU patients** receiving **high doses of CMS** for **more than seven days**, CMS **was not a risk factor for AKI**, and the **presence of septic shock** and **severity of the patients' illness** as reflected by the SAPS II score was **strongly related to the development of AKI**.

Sorli et al. : patients receiving 3–9 million units/day CMS, the prevalence of acute kidney injury (AKI) was 25.5 % and 49 % at day 7 and at the end of treatment (EOT) day. At **day 7**, the only **independent predictor of AKI was the minimum concentration (C min)** of drug with a **breakpoint of 3.33 mg/L**.

At EOT, **independent** risk factors for **AKI** were the **Charlson score**, **C min a the breakpoint of 2.42 mg/L** and **co-administration of≥2 nephrotoxic drugs.**

Pogue et al. : retrospective study, in which **nephrotoxicity** was **described** as a ***dose dependent* rapid onset (within first week)** adverse effect of colistin, there was *30 % increased risk of toxicity* in patients *receiving 3 to 4.9 mg/kg/day* (based on IBW), and *69 % for whom≥5 mg/kg/day* of the drug was administered. They also found that **rifampin co-administration** can **increase** the **risk of nephrotoxicity** by **more than three times**, but there was no increased risk of nephrotoxicity with aminoglycosides in their analyses. Lastly,independent predictors for nephrotoxicity in this study were **colistin dose of≥5.0 mg/kg** of **ideal body weight per day**, receipt of **concomitant rifampin**, and **co-administration of ≥ 3 concomitant nephrotoxins**.

Kwon et al. : retrospective study, **independent predictors** of **colistin nephrotoxicity** were **male sex**, **co-administration** of **calcineurin inhibitors** , **hypo albuminemia** and **Hyperbilirubinemia**.

Doshi et al :retrospective study /the rate of **nephrotoxicity** was **15 %** and patients with **chronic kidney disease** and **hypertension** and who had **received contrast material** had **higher risks of nephrotoxicity**; the risk was also 6.5 times higher in patients with co-administration of≥2 nephrotoxic drugs compared to those without other nephrotoxic agents.

- Ultimately, **risk factors** of **colistin nephrotoxicity** can be categorized as dose and duration of colistin therapy, co-administration of other nephrotoxic drugs, and patient related factors such as **age**, **sex**, **hypoalbuminemia**, **hyperbilirubinemia**, **underlying diseases** and **severity** of the **patients' illness**.

Renal dose adjustment:

- little data about renal dose adjustment of a high dose colistin regimen is available.

Dalfino and colleagues :suggested a new dose adjustment for high dose colistin therapy as follows:

1) patients with creatinine clearance of **20–50 mL/min** after a **loading dose** of **9 MIU**, **maintenance doses of 4.5 MIU every 24 hours** were administrated,
2) patients with creatinine clearance **of<20 mL/min** after a **loading dose of 9MIU**, **maintenance doses of 4.5 MIU every 48 hours** were administrated .

Table 2 Renal dose adjustment suggestion for high dose colistin therapy

IV CMS dosing guideline for the treatment of MDR Gram-negative infections in a systematic review by Visser Kift et al. [46]

	Patient category	Dosing suggestion
Loading dose	Critically ill or severe sepsis	9–12 MIU*
Maintenance dose	eGFR > 60 ml/min	4.5 MIU 12-hourly
	eGFR 30–60 ml/min	3 MIU 12-hourly
	eGFR 10–30 ml/min	2 MIU 12-hourly
	eGFR < 10 ml/min	1 MIU 12-hourly
	Intermittent hemodialysis	1 MIU 12-hourly plus supplemental dose of 1 MIU after each episode of dialysis
	Continuous renal replacement therapy (CRRT)	4.5 MIU 12-hourly

IV CMS dosing guideline (in mg/kg IBW of CBA) in the text book of "Principles and Practice of Infectious Diseases" by Mandell et al. [5]

	Patient category	Dosing suggestion
Loading dose (maximum 300 mg CBA)	All groups	5 mg/kg×1 dose
Maintenance dose	ClCr ≥ 50 (mL/min), start 8 hour after load	5 mg/kg/day divided every 8 hour
	ClCr 30–49 (mL/min), start 12 hour after	3.5 mg/kg/day divided every 12 hour
	ClCr 10–29 (mL/min), start 12 hour after	2.5 mg/kg/day divided every 12 hour
	ClCr < 10 (mL/min) *OR* hemodialysis, started 24 hour after	1.5 mg/kg every 24 hour

* Loading dose is calculated according to ideal body weight (IBW): 12 MIU CMS for 70 kg and 9 MIU for 55 kg patients

CBA colistin base activity; ClCr clearance of creatinine; CMS colistimethate sodium; eGFR estimated glomerular filtration rate; IV intravenous; IBW ideal body weight; MDR multidrug resistant

In **patients** with **continuous renal replacement therapy**, as mentioned in Table 2, due to efficient clearance of both CMS and colistin by venovenous hemofiltration and hemodialysis, a supplemental dose of colistin is needed after dialysis and higher doses are required in patients undergoing venovenous hemofiltration; as **Garonzik et al**. recommends, **higher daily doses of 16MU are required**, as both CMS and colistin are filtered during renal replacement therapy .

In patients without renal problems, **CMS** clearance is **predominantly via renal excretion** and only a **small fraction of the dose is converted to colistin** with effective antibacterial activity.

- Colistin undergoes very **extensive renal tubular reabsorption** and its **clearance** is dominantly via **non-renal mechanisms**, and an **extremely low fraction** of it is **excreted as unchanged in urine.**
- In patients with **renal impairment** but **without CRRT**, a **decrease** of **creatinine clearance and a higher CMS concentration** lead a **larger fraction of CMS** to ***be converted to colistin***, which **necessitates dose adjustment** .
- In contrast, following clearance by diffusion and/or convection in a CRRT cartridge, there is no carrier mediated mechanism to return colistin from dialysate to the blood perfusing the cartridge; therefore, CMS and colistin will be efficiently cleared.

CONCLUSION

- Colistin is a **nephrotoxic** antibiotic/Nephrotoxicity is the concerning adverse effect of this drug, especially with the newly recommended high-dose regimen / nephrotoxicity seems to be **dose-dependent andreversible** .
- The mechanism of nephrotoxicity is via an **increase in tubular epithelial cell membrane permeability**, which results in cations, anions and water influx leading to cell swelling and cell lysis.
- There are also **oxidative and inflammatory pathways** that seem to be **involved in colistin nephrotoxicity**.

Biomarkers for detection of nephrotoxicity:

- little data is available about **best biomarker** for **early detection** of colistin nephrotoxicity.
- Use of the **serum creatinine level** for estimation of the glomerular filtration rate (**GFR**) has some limitations, such as dependence on sex, age, nutrition and body mass.
- In studies on colistin nephrotoxicity, **serum creatinine** and **RIFLE criteria** are **usually used for detection of nephrotoxicity**.
-

Trial by **Shavit et al**. : used urine neutrophil gelatinase-associated lipocalin (**NGAL**) for **early detection of acute kidney** injury of colistin for treatment of urinary tract infection **(UTI)**; in conclusion, they **could not demonstrate a significant increase of urinary NGAL in either ATN or non-ATN groups of patients**; the limitation of their findings with regard to the predictive value of urinary NGAL is probably due to the influence of UTI on NGAL levels in patients with or without kidney diseases.

- NGAL is a protein of the **lipocalin** family and its **expression** is *detected predominantly in proliferating cell nuclear antigen-positive proximal tubule cells*. NGAL is detected in the urine within 3 hours of ischemic injury in both mouse and rat models of renal failure and within 1 day in a nephrotoxic model in mice.

Ghlissi et al. :

study in an animal model of colistin nephrotoxicity, evaluation of change of plasma Cystatin C, along with urinary neutrophil gelatinase associated lipocalin (NGAL),g-glutamyltransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate (AST) and alanine (ALT) aminotransferase for monitoring of colistin nephrotoxicity, was carried out and the results were compared with histopathological assessment. The results of the study showed that **plasma Cystatin C** is more accurate than **plasma creatinine** and urinary NGAL is the most sensitive biomarker for detection of colistin nephrotoxicity .

- Cystatin C is a **cysteine protease inhibitor** that is synthesized by all nucleated cells and **freely filtered by the glomerulus**, **reabsorbed completely in proximal tubules,** and **not secreted**. The levels of cystatin C are not affected by gender, age, race or muscle mass .

Keirstead et al. :

- using an animal model, the accuracy of some urinary biomarkers for the detection of AKI in polymixin-induced nephrotoxicity was evaluated. In this study, **kidney injury molecule 1 (KIM 1)** and **α-GST** were the most sensitive biomarkers for **prediction of polymixin-induced nephrotoxicity**.
- **Kim-1** is a **phosphatidylserine receptor** that is **expressed in normal proximal tubula epithelial cells**; its mRNA levels are elevated following acute tubular injury. Urinary Kim-1 has been reported to be specific to proximal tubular damage.

Prevention of colistin nephrotoxicity:

Oxidative damage attributed to colistin is suggested as a mechanism of nephrotoxicity. In a study in rat model, a comparison of colistin and colistin with N-acetyl cysteine (NAC) groups was carried out. ***NAC reduced renal tissue superoxide dismutase (SOD),*** **reverse staining** of inducible nitric oxide synthase **(i-NOS)** and **neutrophin-3**, and significantly reduced immunostaining of endothelial NOS **(e-NOS)** and **i-NOS in lung tissue**; therefore, **administration of colistin with NAC probably decreases oxidative damage of colistin**, although NAC did not significantly improve biochemical value and creatinine clearance.

Ozkan et al.:

effect of colistin on caspase 1 and 3, i-NOS and e-NOS staining was assessed in rat model/ administration of grape seed proanthocyanidin extract (**GSPE) with colistin significantly diminished BUN and creatinine levels**, renal histopathological score, caspase 1 and 3, calpain 1, i-NOS and e-NOS staining compared to in the colistin alone group.

GSPE is a natural substance with antioxidant, antiapoptotic, anticarcinogenic, vasodilator and anti-inflammatory effects, which is obtained from black grape and has shown **renoprotective** effects in previously designed AKI models. The author has suggested that its mechanism in preventing colistin renal injury is an ***antiapoptotic effect via reducing caspase 3 levels***, and an ***antinecrotic*** effect via ***reducing calpain 1 and caspase 3 levels*** .

Yousef et al.:

the effect of melatonin on colistin nephrotoxicity in animal model was investigated /a significant increase in creatinine levels and significant histological abnormalities were observed only in colistin group compared with colistin with melatonin. **Significantly lower urinary** N-acetyl-b-D-glucosaminidase (**NAG**) excretion, as a **marker of tubular damage**, was observed f**rom day 1 in the colistin-melatonin group** compared to the **colistin group,** which is an indicator of **tubular cell injury**. (Histological changes were seen in all rats in the colistin group and **included acute tubular necrosis** and **acute cortical necrosis**, compared with only one rat in each of the other groups (control, melatonin, and colistin-melatonin), which showed mild focal tubular changes .)

Yousef et al:

the protective effect of Ascorbic acid on nephrotoxicity of colistin in rats was examined. **High dose (200 mg/kg twice a day**, approximately **equivalent to the 2 g/day** for a 60 kg adult by the Food and Nutrition Board) and **low dose ascorbic acid** showed **nephroprotective** effects in histological findings. All rats in the ***colistin alone*** group had *severe tubular damage and tubular epithelial cell necrosis & tubular casts*, compared with only one rat in the low dose ascorbic acid with colistin group, which showed mild focal tubular changes. Monitoring of N-acetyl-b-D-glucosaminidase (**NAG**) as a **marker of tubular damage** also confirmed histological findings in this study.

- Ghlissi et al.'s study: **co-administration** of **colistin with vitamin E** or ***astaxanthin*** had some benefit via its antioxidant activity. **Astaxanthin** is a **red-orange carotenoid** with antioxidant and anti inflammatory properties, and is found naturally in a wide variety of aquatic organisms, such as microalgae, fishes, and crustaceans such as shrimps.

WHATS NEW?

Dose Optimization of Colistin: A Systematic Review /2021

Colistin is considered a last treatment option for multi-drug and extensively resistant Gram-negative infections. A systematic review was performed to identify all published studies on the dose optimization of colistin. Grey literature and electronic databases were searched. Data were collected in a specified form and the *quality of the included articles was then assessed using the Newcastle-Ottawa scale* for cohort studies, the **Cochrane** bias tool for randomized clinical trials (**RCT**), and the Joanna Briggs Institute (**JBI**) critical checklist for **case reports**. A total of 19 studies were included, of which 16 were cohort studies, one was a RCT, and two were case reports.

- A total of 18 studies proposed a dosing regimen for adults, while only one study proposed a dosing schedule for pediatric populations. As per the available evidence, a loading dose of **9 (MIU)** of colistin followed by a maintenance dose of **4.5 MIU every 12 h** was considered the **most appropriate** dosing strategy to optimize the safety and efficacy of treatment and improve clinical outcomes. *This review supports the administration of a loading dose followed by a maintenance dose of colistin in severe and life-threatening multi-drug Gram-negative bacterial infections.*

- A study documented the significance of the appropriate use of antibiotics and the need to incorporate PK/PD data into dosage scheduling. This review provided the available evidence evaluating the **dosing strategy** of **colistin among critically ill patients**. Regarding the changes in dosing strategies, **studies showed that a loading dose may help to minimize the risk of colistin associated nephrotoxicity**.

- Front loading is **considered** the optimal dosing strategy, which maximized the therapeutic outcomes and minimized the risk of side effects .The European Society for Clinical Microbiology and Infectious diseases (ESCMID) recommended a daily dose of colistin base activity **(CBA) of 9–10.9 MIU,** divided **into two and infused over 0.5–1 h at a 12-h** interval in patients with **normal renal function**, in order to achieve the desired therapeutic outcomes.
- The **CBA dose adjustment** is made according to **creatinine clearance** in patients with **renal impairment**.

- **Inappropriate** dose adjustment could **result in** *elevated plasma concentration of a drug, leading to adverse drug reactions, and thus* ***increasing the risk of mortality, morbidity, and increased length of hospital stay*** .
- **Nephrotoxicity** and **neurotoxicity** are the most substantial and frequent adverse effects of polymixins .In pediatrics, the **loading dose** of **4mg of CBA/kg** is beneficial for the improvement of drug exposure, by **increasing** the area under curve **(AUC)** and maximum plasma concentration (Cmax) **without AKI**.

- The prevalence of **colistin-associated nephrotoxicity** ranges from **0.6%** to **10%** in the pediatric population . On the basis of **RIFLE** (risk, injury, failure, loss of kidney function, end-stage kidney disease) **criteria**.

- A study reported a **high prevalence rate of nephrotoxicity** in a higher dose group (60%) than in a conventional dose group (20%).

Colistin Nephrotoxicity:Meta-Analysis of Randomized Controlled Trials / 2023

- Article: Open Forum Infectious Diseases
- By : Khalid Eljaaly, Monique R. Bidell, Ronak G. Gandhi, Samah Alshehri,Mushira A. Enani, Ahmed Al-Jedai, and Todd C. Lee

- Colistin remains a clinically relevant polymyxin agent. In a meta-analysis of RCTs, the incidence of **colistin-associated nephrotoxicity** was approximately **36%** and the relative risk compared with β-lactams increased by 140%. This analysis had low heterogeneity and characterized risk associated with contemporary colistin dosing recommendations. Clinicians should weigh the risks versus benefits of using colistin therapy given its toxicity potential in critically ill patients.

Renal dose adjustement for prescribtion of colistin

Medscape

Dosage Forms & Strengths

powder for injection

- 150mg/vial

Susceptible Infections

Dosage expressed in terms of colistin base

2.5-5 mg/kg/day divided q6-12hr IV/IM; not to exceed 5 mg/kg/day

Renal Impairment

CrCl >80 mL/min: No dosage adjustment required

CrCl 50-79 mL/min: 2.5-3.8 mg/kg/day IV/IM divided q12hr

CrCl 30-49 mL/min: 2.5 mg/kg/day IV/IM qDay or divided q12hr

CrCl 10-29 mL/min: 1.5 mg/kg IV/IM q36hr

Other Indications & Uses

Gram-neg. infection (e.g., Enterobacter aerogenes, E. coli, Klebsiella, Pseudomonas) unresponsive to other antibiotics

Multi-drug resistant gram-neg. infection

DRUGS·COM (2023 update)

Usual Adult Dose for Gram Negative Infection

Parenteral: 2.5 to 5 mg/kg/day IM or IV in 2 to 4 divided doses, depending on severity of infection
Maximum dose: 5 mg/kg/day

Comments:

- The dosage is expressed in terms of colistin base.
- Clinical effectiveness has been shown in the treatment of infections due to Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

Approved indication: Treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli (particularly infections due to P aeruginosa); not indicated for infections due to Proteus or Neisseria

Some experts recommend:
Inhalation: 50 to 75 mg in normal saline (3 to 4 mL total volume) via nebulizer 2 to 3 times a day

Renal Dose Adjustments

Colistimethate should be used with extreme caution in the presence of renal dysfunction.

Suggested modification for adults:

Normal renal function (CrCl 80 mL/min or greater): 2.5 to 5 mg/kg/day IM or IV in 2 to 4 divided doses

Mild renal dysfunction (CrCl 50 to 79 mL/min): 2.5 to 3.8 mg/kg/day IM or IV in 2 divided doses

Moderate renal dysfunction (CrCl 30 to 49 mL/min): 2.5 mg/kg/day IM or IV in 1 to 2 divided doses

Severe renal dysfunction (CrCl 10 to 29 mL/min): 1.5 mg/kg IM or IV every 36 hours

If signs of impaired renal function occur (including decreased urine output, rising serum creatinine and BUN, and decreased CrCl): Colistimethate should be discontinued at once.

UP TO DATE

Dosing: Renal Impairment

Note: Dosage expressed in terms of **colistin base activity (CBA);** although reported conversions have varied slightly in the literature, **CBA 1 mg** is defined to be equivalent to **colistimethate sodium (CMS) 30,000 units** (Falagas 2006).

IM, IV: Adults:

Manufacturer's labeling:

CrCl ≥80 mL/minute: No dosage adjustment necessary; maximum: 5 mg CBA/kg/day

CrCl 50 to 79 mL/minute: 2.5 to 3.8 mg CBA/kg/day in 2 divided doses

CrCl 30 to 49 mL/minute: 2.5 mg CBA/kg/day once daily or in 2 divided doses

CrCl 10 to 29 mL/minute: 1.5 mg CBA/kg every 36 hours

Alternative recommendations:

Severe infections (due to multidrug-resistant organisms susceptible to colistin in the critically ill) (Dalfino 2012): **Note:** CrCl calculated using the Cockcroft-Gault equation. IV:

CrCl ≥50 mL/minute: Loading dose of 300 mg CBA followed by 150 mg CBA twice daily.

CrCl 20 to 50 mL/minute: Loading dose of 300 mg CBA followed by 150 mg CBA once daily.

CrCl <20 mL/minute: Loading dose of 300 mg CBA followed by 150 mg CBA every 48 hours.

May also consider using the following calculations; however, although derived from critically ill patients, the use of this algorithm has not been prospectively evaluated in the critically ill (Garonzik 2011):

Loading dose of colistin base activity (mg) = Target average colistin steady-state plasma concentration (in mg/L) x 2 x weight (in kg). For patient weight, use the lower of ideal or actual body weight expressed in kg. In obese patients, application of these equations has not been evaluated.

Daily maintenance dose of colistin base activity (mg) = Target average colistin steady-state plasma concentration (in mg/L) x ([1.5 x CrCl] + 30)

Note: Use caution with loading doses >300 mg CBA. Do not exceed a total daily dose of 300 mg CBA (according to this algorithm). Target $C_{ss,avg}$ is typically 2.5 mg/L but may range from 2 to 4 mg/L (Couet 2012). Calculate CrCl using the Jellife method mL/minute/1.73 m^2 or the Cockcroft-Gault method (normalized to BSA of 1.73 m^2).

CrCl >70 mL/minute/1.73 m^2: Administer calculated daily maintenance dose in 2 to 3 divided doses every 12 or 8 hours, respectively. **Note:** Unless it is appropriate to target a low colistin $C_{ss,avg}$, the authors do not recommended the use of these calculations in patients with CrCl >70 mL/minute/1.73 m^2.

CrCl 10 to 70 mL/minute/1.73 m^2: Administer calculated daily maintenance dose in 2 to 3 divided doses every 12 or 8 hours, respectively.

CrCl <10 mL/minute/1.73 m^2: Administer calculated daily maintenance dose in divided doses every 12 hours.

Intermittent hemodialysis (IHD) (administer after hemodialysis on dialysis days): IV: 1.5 mg CBA/kg every 24 to 48 hours (Heintz 2009). **Note:** Dosing dependent on the assumption of 3 times/week, complete IHD sessions. Alternatively, may administer a daily dose of 30 mg CBA for every 1 mg/L colistin $C_{ss,avg}$ target given in divided doses every 12 hours on nonhemodialysis days. For example, if the $C_{ss,avg}$ target is 2.5 mg/L, then administer 37.5 mg CBA every 12 hours on nonhemodialysis days. On hemodialysis days (ideally performed at the end of the colistin dosage interval), administer a supplemental dose of 50% of the total daily dose if the supplemental dose is administered during the last half hour of the hemodialysis session **or** 30% of the total daily dose if the supplemental dose is administered after the hemodialysis session. These recommendations, although derived from critically ill patients, have not been prospectively evaluated in the critically ill (Garonzik 2011).

Continuous renal replacement therapy (CRRT) (Heintz 2009; Trotman 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 to 2 L/hour and minimal residual renal function) and should not supersede clinical judgment:

THANKS FOR YOUR ATTENTION